

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/006534

International filing date (day/month/year)
17.06.2004

Priority date (day/month/year)
20.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68, C07H21/00, A61K31/712

Applicant
EPIGENOMICS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/006534

10/562023

Box No. I Basis of the opinion

IAP20 Rec'd 17 DEC 2005 2.0 DEC 2005

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-22
	No: Claims	
Inventive step (IS)	Yes: Claims	1-22
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-19,22
	No: Claims	20,21

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

10/562023
IAP20 Rec'd PCT/EP 20 DEC 2005

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited documents

- 1.1 The documents mentioned in this written opinion are numbered as in the International Search Report i.e. D1 corresponds to the first document of the search report etc.

2. Novelty (Articles 33(2) PCT)

- 2.1 The present application satisfies the criterion set forth in Article 33(2) PCT because the subject matter of claims 1-22 is new in respect to the prior art as defined in the regulations (Rule 64(1)-(3) PCT).
- 2.2 None of the available prior art documents disclose the use of triplex forming oligonucleotides in a method for detecting methylated cytosines. Consequently, the subject-matter of claim 1 appears to be novel (Article 33(2) PCT).
- 2.3 Claims 2-17 are dependent on claim 1 and, as such, also meet the requirements of the PCT with respect to novelty (Article 33(2) PCT).
- 2.4 Furthermore, the prior art does not disclose the subject-matter of independent claims 18-22. Therefore, said subject-matter must also be considered novel (Article 33(2) PCT).

3. Inventive step (Article 33(3) PCT)

- 3.1 The present application also satisfies the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-22 involves an inventive step with respect to the available prior art (Rule 65(1)(2) PCT).
- 3.2 Document D1, which can be considered as the closest prior art to the subject-matter of claim 1, describes a method of detecting cytosine methylation by performing PCR on a DNA sample in which all non-methylated cytosines have been chemically modified to uracil. The difference between D1 and the subject-matter of claim 1 is that the applicants have used triplex forming oligonucleotides comprising chemically modified bases which can distinguish between methylated

and unmethylated cytosines to detect cytosine methylation. The apparent technical problem can therefore be considered as to provide an alternative method for distinguishing methylated DNA from unmethylated DNA. Although documents D2 and D3 describe stable DNA triplex formation using oligonucleotides containing derivatives of cytosine, in particular, N⁴-(3-acetamidopropyl)cytosine and N⁴-(6-amino-2-pyridinyl)deoxycytidine, there is no suggestion in said documents that the therein described oligonucleotides would preferentially bind to unmethylated cytosines as opposed to methylated cytosines. Consequently, the solution to the apparent technical problem, as stated in claim 1, would not be obvious and would require inventive effort on behalf of the skilled person. Therefore, claim 1 appears to meet the requirements of Article 33(3) PCT.

3.3 Claims 2-17 are dependent on claim 1 and, as such, also meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT).

3.4 The reasoning stated in item 3.2 above is also applicable *mutatis mutandis* to independent claims 18-22. Therefore, claims 18-22 also appear to be inventive (Article 33(3) PCT).

4. Industrial Applicability (Article 33(4) PCT)

4.1 Claims 20 and 21, as far as *in vivo* methods are concerned, can be considered as methods of treatment. For the assessment of claims 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. Claims 1-4, and 10-21 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely

amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.